## REMARKS

**Rejection of Claims and Traversal Thereof**

In the December 3, 2004 Office Action,

claims 1-14 were rejected under 35 U.S.C. §112, second paragraph; and

claims 1-14 were rejected under 35 U.S.C. §112, first paragraph.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

**Rejection under 35 U.S.C. §112, second paragraph**

In the December 3, 2004 Office Action, claims 1 -14 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants have amended independent claim 1, and dependent claims 7 and 14 thereby obviating the rejection. Withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

**Rejection under 35 U.S.C. §112, first paragraph**

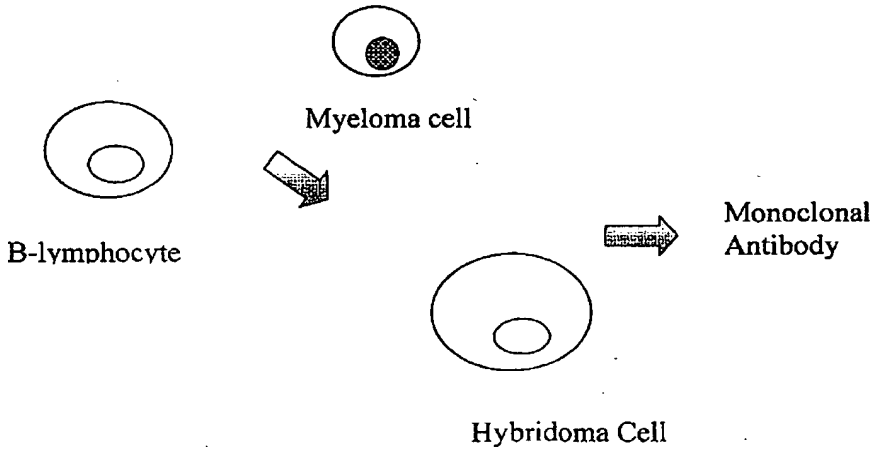
Claims 1-14 were rejected under 35 U.S.C. §112, first paragraph. According to the Office, the disclosure fails for several reasons. For completeness, applicants will address each of the Office's remarks and contentions individually.

1. Claims 1-14 were rejected under 35 U.S.C. §112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention. According to the Office:

> "applicant's specification provides no written description or guidance for inhibiting the uptake of secreted antibodies by undesired nonsecreting cells in the population having the instantly disclosed antibody binding molecules

> expressed thereon. Thus, one would not be assured of the ability to select the desired producer cell(s) from the population because, absent further guidance from applicant, one would be unable to identify and specifically separate the secreting cell(s) from a population of cells which are all capable of binding the secreted product."

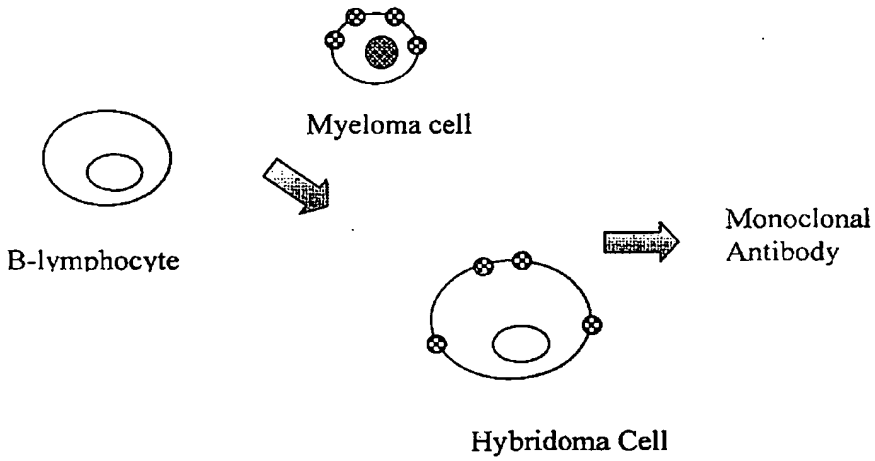
Applicants vigorously disagree. Initially, it should be noted that the method of hybridoma technology according to Kohler and Milstein is shown below in Figure 1




This 30 year old method provides for a tumor cell that does not secrete antibodies which is fused to a non-tumor B-lymphocytes that codes for one (1) specific antibody. The resulting hybridoma cell grows indefinitely (like its ancestor tumor cell) and it secretes one defined monoclonal antibody with one antigen specificity (from its ancestor B-lymphocyte). Selection of hybridoma cells is done with a selective medium: wherein B-lymphocytes will die in a few weeks, mutated myeloma cells will not grow in HAT medium. However, hybridoma cells do grow on the HAT medium because the B-lymphocytes' fusion repairs the mutated myeloma.

As stated in the specification, this 30 year old method has some drawbacks because the fusion and selection of hybridomas is laborious. Thousands of single cells are grown to clone size and their supernatant checked for the desired secreted antibodies. Further, directly after the fusion, hybridoma cells are extremely unstable and the majority of the hybridoma cells loose their antibody genes and don't secret antibodies, so it is very important to attend to the cloning very quickly.

The present invention overcomes the shortcomings of this 30 year old method by introducing an antibody-binding protein into the myeloma cell BEFORE THE FUSION TO THE B-LYMPHOCYTE. This is easily accomplished by introducing a coding vector into the original myeloma cell. Then a stable myeloma-subcell-line is selected that presents multiple antibody-binding proteins on its surface so that many antibodies can be glued to the surface once this myeloma is fused and forms the hybridoma. Accordingly, single cells report their status, e.g. in a FACs machine instead of waiting for cell clones that secrete antibodies into the supernatant.




Importantly, during the critical time, when the hybridoma is unstable, thousand of clones or subclones do not have to be grown, nor does not a researcher have to wait until antibodies accumulate in the supernatant in sufficient numbers to analyze. Instead, analysis of single cells that secrete and present antibodies is accomplished by FACS.

Clearly, a viable hybridoma has to express both the antibody binding protein from the myeloma cell and the antibody from the spleen cell. As stated in the specification at page 11, the cell fusion mixture is cultured in a HAT medium and it is well known in the art that unfused myeloma cells cannot grow in HAT because they lack HGPRT and unfused normal spleen cell cannot grow for any length of time because they have a limited life span. However, successful fusion produces a hybridoma cell that is able to generate both the antibody binding protein and an antibody expressed on the surface and adhering to the antibody binding protein. If the proper fusion does not occur, then the hybridoma cell will not survive to generate either the antibody binding protein or the antibody.

Importantly, this secretion of antibodies and presentation occurs in a system wherein one cell is placed in one well and grown according to the HAT medium discussed above. Clearly, there is no likelihood that a non-secreting cell presents antibodies from another secreting cell because we are discussing a system with one cell per well. It either secrets antibodies and presents same or it does not. As such, applicants suggest that the concern by the Office regarding the possibility of secreted antibodies being taken up by non-secreting hybridoma cell is unwarranted and likely impossible.

It is well settled in the law that the disclosure includes not only that which is expressly set forth in words, but also that which would be understood by persons skilled in the art. As such, applicants may begin at the point where the invention begins, and describe that which is new. That which is old and well known is as if written out in the patent. Clearly, applicants should not have to explain to one skilled in the art the logistics of successful fusions to generate hybridoma cells that grow indefinitely because the spleen cell partner supplies HGPRT and the myeloma partner is immortal.

Further, applicants submit that one skilled in the art after reading the specification would clearly understand that the myeloma cells are engineered in order to express a large amount of antibody binding proteins on their surface. Thereby, antibodies are trapped on the surface of their descendent hybridoma cells that now are easily sorted in FACS, obviating most of the laborious screening and subcloning needed in conventional hybridoma technology. Sorting by FAC provides for quick identification of hybridomas through different fluorescence patterns. Monoclonal antibodies, tagged with a fluorescent dye (typically fluorescein or phycoerythrin), are bound specifically to the cells and as the individual cells pass through a laser light, the light is scattered, and the fluorescent dye becomes excited by the laser beam causing the tagged cells to emit fluorescence. Photocells then send signals to the CPU characterizing each of the cells. Cells that display the desired "photo characteristics" are collected. The examples set forth in the specification clearly describe the present invention.

Notably, the Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discarded by "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim*, 191 USPQ 90 (CCPA 1976). Further, if the specification contains a description of

the claimed invention, albeit not in *ipsis verbis*, then the Office, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient. Applicants assert that one of ordinary skill in the art would find that the present specification provides a clear and concise description of the present invention.

Accordingly, applicants respectfully request this rejection under 35 U.S.C. §112, first paragraph for lack of written description be withdrawn.

2. Claims 1-6 and 9-14 were rejected under 35 U.S.C. §112, first paragraph, because, according to the Office, the specification does not reasonably provide enablement for expression of cell-surface antibody binding proteins, generally other than those expressed by the particular exemplified expression vectors which function in the invention.

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. See *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 109 S.Ct. 1954 (1989); *In re Stephens*, 188 USPQ 659, 661 (CCPA 1976). In making a rejection on the ground of nonenablement, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The Office has stated that stable cell surface expression of the antibody binding protein in the myeloma cell or hybridoma is unpredictable because of the random shedding of genetic elements from hybridomas. Applicants are well aware of this problem that is inherent in the Kohler and Milstein method. Specifically, that fusion hybridomas are unstable and that they tend to discard genetic material by trying to reduce their 4x-chromosome-set to the normal 2x-chromosome-set. Even more of a problem is the time it takes for a sufficient amount of antibodies to be secreted so

that a sufficient number is produce for determination in the supernatant. The current invention overcomes these problems because as soon a few antibodies are secreted and presented by the antibody binding protein a desirable hybridoma is recognized.

Applicants submit that the specification provides guidance regarding the antibody binding protein and states expressly that this protein must bind an antibody and present same on the cell surface of the hybridoma cell. Expression of the protein on a myeloma cell is within the ability of one skilled in the art. Further, preparing a hybridoma cell that expresses both an antibody and the antibody binding protein is easily accomplished by following the instructions set forth in the examples of the specification. Applicants have not included an example for each and every possible variant of the antibody binding protein but it is well settled in the law that a working example is not required for every single embodiment of the invention, especially if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice (See *In re Borkowski*, 164 USPQ 642 (CCPA 1970) and *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Thus, the breath of the claims is not broader than that described in the specification and the quantity of experimentation to practice the full scope of the claims does not require undue experimentation.

The issue raised by the Office seems to relate to whether one skilled in the art could make and use the claimed invention without undue experimentation. Applicant submits that the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeal summarized the point well when it stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." *Ex parte Jackson*, 217 USPQ 804, 807 (1982).

Here, all the Office has established is that some experimentation would be required to make and use other embodiments of the claimed invention. What the Office has not done is to perform the fact-finding needed in order to reach a proper conclusion of undue experimentation.

The specification provides ample guidance for determining the expression of transfected expression vectors and successful generation of hybridoma cells. It should be noted that claim 1 and all claims depending therefrom defines parameters that enable broader antibody binding proteins because the claims recites functional language that clearly defines the functional activity of the antibody binding protein. According to the court in *In re Marks*, 12 USPQ2d 1904 (BPAI 1989) with the addition of functional language, one skilled in the art would be able to determine in a routine fashion, without undue experimentation whether the antibody binding protein is expressed and functionally active. The functional activity can be very easily determined by one skilled in the art, and the specification provides guidance as set forth in Examples 1 and 2. Thus, the breath of the claims is not broader than that described in the specification and the quantity of experimentation to practice the full scope of the claims does not require undue experimentation.

Clearly, the level of skill in this field is very high, and as such, information known by one skilled in the art will provide ample assistance in practicing the claimed invention and contribute significantly to the enabling scope of the disclosure. Applicants request that this rejection under 35 U.S.C. §112, first paragraph for lack of enablement be withdrawn.

3. Claim 1-14 were rejected under 35 U.S.C. §112, first paragraph, because the specification does not provide evidence that the claimed biological materials are: (1) know and readily available to the public, (2) reproducible from the written description; or (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. Applicants vigorously disagree and submit that the present specification provides ample guidance for recreating the expression vectors as shown in Figures 1, 2, and 3. The nucleotide sequence is defined in SEQ ID NOs. 1, 3 and 5. As such, one can easily synthesize the DNA molecules and insert same in an appropriate expression vector.

Notably, to demonstrate the lack of enablement, the Office must demonstrate that one of skilled in the art cannot, without undue experimentation, practice the claimed methods. Further, even if some experimentation may be involved in practicing the invention, it is well settled that the enablement requirement permits some experimentation, so long as that experimentation is not

undue. In *PPG Indus., Inc., v. Guardian Indus. Corp.*, 27 USPQ2d 1618, 1623 (Fed. Cir. 1996), the court stated that even where some experimentation is necessary to reduce an invention to practice, the enablement requirement is satisfied where: (1) the experimentation is routine; or (2) the specification provides "a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. Applicants' specification meets these guidelines because the nucleotide sequences for the expression vectors are included in the specification and can be easily synthesized. The technology required to express a nucleotide sequence in myeloma cell is no longer unpredictable and the techniques used for successful insertion of an expression vector in a cell line are well known and taught in most undergraduate molecular biology courses. Further fusion techniques for fusing of a myeloma cell and a normal spleen cell which secrets a desired antibody are also well known in the art.

Applicants submit that the instant application provides sufficient and enabling information for a person of ordinary skill in the art to practice applicants' invention and respectfully request the withdrawal of all rejections under §112, first paragraph.

**Petition for Extension of Time and Fees Payable**

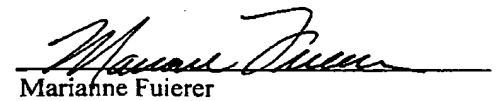
Applicants hereby petitions for a two (2) month extension of time, extending the deadline for responding to the December 3, 2004 Office Action from March 3, 2005 to May 3, 2005. The entry of this petition results in a petition fee of $225.00. A credit card authorization form in the amount of $225.00 is included herein for payment of the petition fee.

Applicants have cancelled herein one independent claim and 4 dependent claims. Applicants have added one new independent claim and 3 new dependent claims. No fees are due for the addition of the new claims. In the event a fee is found due for entry of this amendment, authorization is hereby given to charge any deficiency in applicable fees for this response to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

**Conclusion**

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Grun reconsider the patentability of all pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Grun is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,



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